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CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200312

ED Entered STN: 20031028  
Last Updated on STN: 20031225  
Entered Medline: 20031224

AB Insulin-like growth factor (IGF)-I is a pleiotropic hormone that regulates vascular smooth muscle cell (VSMC) migration, proliferation, apoptosis, and differentiation. These actions are mediated by the IGF-I receptor. How activation of the same receptor by the same ligand leads to these diverse cellular responses is not well understood. Here we describe a novel mechanism specifying VSMC responses to IGF-I stimulation, distinctive for the pivotal roles of local IGF-binding proteins (IGFBPs). The role of local IGFBPs was indicated by comparing the activities of IGF-I and des-1-3-IGF-I, an IGF-I analog with reduced binding affinity to IGFBPs. Compared with IGF-I, des-1-3-IGF-I was more potent in stimulating DNA synthesis but much less potent in inducing directed migration of VSMCs. When the effects of individual IGFBPs were tested, IGFBP-2 and IGFBP-4 were found to inhibit IGF-I-stimulated DNA synthesis and migration. IGFBP-5 had an inhibitory effect on IGF-I-stimulated DNA synthesis, but it strongly potentiated IGF-I-induced VSMC migration. By using a non-IGF-binding IGFBP-5 mutant and an IGF-I-neutralizing antibody, it was demonstrated that IGFBP-5 also stimulates VSMC migration in an IGF-independent manner. This effect of **IGFBP-5** was inhibited by **soluble** heparin and by treating cells with heparinase. Mutation of the heparin-binding motif of IGFBP-5 reduced its migration promoting activity. These findings suggest that local IGFBPs are important determinants of cellular responses to IGF-I stimulation, and a key player in this paradigm is IGFBP-5. IGFBP-5 not only modulates IGF-I actions, but it also stimulates cell migration by interacting with cell-surface heparan sulfate proteoglycans.

L5 ANSWER 3 OF 14 MEDLINE on STN

AN 2003489061 MEDLINE

DN PubMed ID: 14566968

TI Zinc partitions insulin-like growth factors (IGFs) from **soluble** IGF binding protein (**IGFBP**)-5 to the cell surface receptors of BC3H-1 muscle cells.

AU McCusker Robert H; Novakofski Jan

CS Department of Animal Sciences, Laboratory for Developmental Endocrinology, The University of Illinois, Urbana, Illinois 61801, USA..  
rmccuske@uiuc.edu

SO Journal of cellular physiology, (2003 Dec) 197 (3) 388-99.  
Journal code: 0050222. ISSN: 0021-9541.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200312

ED Entered STN: 20031021  
Last Updated on STN: 20031219  
Entered Medline: 20031205

AB Zinc (Zn(2+)) is a multifunctional micronutrient. The list of functions for this micronutrient expanded with the recent discovery that Zn(2+) retains insulin-like growth factors binding proteins (IGFBPs) on the surface of cultured cells, lowers the affinity of cell-associated IGFBPs,

=> s 14 (5a) (soluble)  
L5 14 L4 (5A) (SOLUBLE)

=> d 15 1-14 bib ab

L5 ANSWER 1 OF 14 MEDLINE on STN  
AN 2004065862 MEDLINE  
DN PubMed ID: 14765975  
TI Zinc partitions IGFs from **soluble** IGF binding proteins ( **IGFBP**)-5, but not **soluble** **IGFBP**-4, to myoblast IGF type 1 receptors.  
AU McCusker R H; Novakofski J  
CS The Department of Animal Sciences, Laboratory for Developmental Endocrinology, The University of Illinois, Urbana, Illinois 61801, USA..  
rmccuske@uiuc.edu  
SO Journal of endocrinology, (2004 Feb) 180 (2) 227-46.  
Journal code: 0375363. ISSN: 0022-0795.  
CY England: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200404  
ED Entered STN: 20040210  
Last Updated on STN: 20040417  
Entered Medline: 20040416  
AB Zinc (Zn(2+)), a multifunctional micronutrient, was recently shown to lower the affinity of cell-associated insulin-like growth factor (IGF) binding protein (IGFBP)-3 and IGFBP-5 for both IGF-I and IGF-II, but to increase the affinity of the cell surface type 1 IGF receptor (IGF-1R) for the same two ligands. However, there is a need for data concerning the effects of Zn(2+) on soluble IGFBPs and the type 2 IGF receptor (IGF-2R). In the current work, we demonstrate that Zn(2+) affects the affinity of IGFBP-5 secreted by myoblasts but not IGFBP-4. Zn(2+), at physiological levels, depressed binding of both IGF-I and IGF-II to IGFBP-5, affecting (125)I-IGF-I more than (125)I-IGF-II. Both (125)I-IGF-I and (125)I-IGF-II bound to high and low affinity sites on IGFBP-5. Zn(2+) converted the high affinity binding sites of IGFBP-5 into low affinity binding sites. An IGF-I analog, (125)I-R(3)-IGF-I, did not bind to the **soluble** murine **IGFBP**-5. Zn(2+) also decreased the affinity of the IGF-2R on L6 myoblasts. In contrast, Zn(2+) increased IGF-I, IGF-II and R(3)-IGF-I binding to the IGF-1R by increasing ligand binding affinity on both P(2)A(2a)-LISN and L6 myoblasts. **Soluble IGFBP** -5 and **IGFBP**-4 depressed the binding of (125)I-IGF-I and (125)I-IGF-II to the IGF-1R, but did not affect binding of (125)I-R(3)-IGF-I. By depressing the association of the IGFs with **soluble IGFBP**-5, Zn(2+) partitioned (125)I-IGF-I and (125)I-IGF-II from **soluble IGFBP**-5 onto cell surface IGF-1Rs. This effect is not seen when soluble L6-derived IGFBP-4 is present in extracellular fluids. We introduce a novel mechanism by which the trace micronutrient Zn(2+) may alter IGF distribution, i.e. Zn(2+) acts to increase IGF-1R binding at the expense of IGF binding to **soluble IGFBP**-5 and the IGF-2R.

L5 ANSWER 2 OF 14 MEDLINE on STN  
AN 2003501331 MEDLINE  
DN PubMed ID: 12917428  
TI Regulation of vascular smooth muscle cell responses to insulin-like growth factor (IGF)-I by local IGF-binding proteins.  
AU Hsieh Tzefu; Gordon Rebecca E; Clemmons David R; Busby Walker H Jr; Duan Cunming  
CS Department of Molecular, Cellular, and Developmental Biology, the

and increases the affinity of the cell surface insulin-like growth factor (IGF)-type 1 receptor (IGF-1R). However, currently there is no information concerning the effect of Zn(2+) on soluble IGFBPs. In the current study, the **soluble IGFBP-5** secreted by BC(3)H-1 cells is shown to bind approximately 50% more [(125)I]-IGF-II than [(125)I]-IGF-I at pH 7.4. Zn(2+) is shown to depress the binding of both IGF-I and IGF-II to **soluble** secreted **IGFBP-5**; [(125)I]-IGF-I binding is affected more so than [(125)I]-IGF-II binding. Zn(2+) acts by lowering the affinity (K(a)) of IGFBP-5 for the IGFs. Scatchard plots are non-linear indicating the presence of high and low affinity binding sites; Zn(2+) affects only binding to the high affinity site. In contrast, Zn(2+) increases the affinity by which either [(125)I]-IGF-I or [(125)I]-R(3)-IGF-I binds to the IGF-1R, but depresses [(125)I]-IGF-II binding to the IGF-type 2 receptor (IGF-2R) on BC(3)H-1 cells. By depressing the association of the IGFs with soluble IGFBPs, Zn(2+) is shown to repartition either [(125)I]-IGF-I or [(125)I]-IGF-II from **soluble IGFBP-5** onto cell surface IGF receptors. Zn(2+) was active at physiological doses depressing IGF binding to IGFBP-5 and the IGF-2R at 15-20 microm. Hence, a novel mechanism is further characterized by which the trace micronutrient Zn(2+) could regulate IGF activity.

L5 ANSWER 4 OF 14 MEDLINE on STN  
AN 2003166786 MEDLINE  
DN PubMed ID: 12684675  
TI Could exemestane affect insulin-like growth factors, interleukin 6 and bone metabolism in postmenopausal advanced breast cancer patients after failure on aminoglutethimide, anastrozole or letrozole?.  
AU Ferrari Leonardo; Bajetta Emilio; Martinetti Antonia; Celio Luigi; Longarini Raffaella; La Torre Ignazia; Buzzoni Roberto; Gattinoni Luca; Seregini Ettore; Bombardieri Emilio  
CS Nuclear Medicine Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, I-20133 Milano, Italy.  
SO International journal of oncology, (2003 May) 22 (5) 1081-9.  
Journal code: 9306042. ISSN: 1019-6439.  
CY Greece  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200308  
ED Entered STN: 20030410  
Last Updated on STN: 20030812  
Entered Medline: 20030811  
AB Postmenopausal hormone-sensitive breast cancer is currently treated with either antioestrogens or aromatase inhibitors (AIs), due to the clinical efficacy and safety of these drugs. Today's challenge is the sequential use of AIs with different structure and no cross-resistance to improve the therapeutic outcome. The present study describes the biological action of the steroidal structure (SS)-AI exemestane (EXE), in patients progressing on aminoglutethimide (AG) or other non-steroidal structure (NSS)-AIs (letrozole or anastrozole). Thirteen patients were evaluated for serum insulin-like growth factor (IGF) components [total IGF-1, IGF-2 and IGF binding protein (**IGFBP**)-3], interleukin (IL)-6 system [IL-6 and **soluble** IL-6 receptor (sIL-6-R)] and bone metabolism markers [bone gla protein/osteocalcin (BGP), bone-specific isoform of alkaline phosphatase (BAP) and carboxy-telopeptide of type I procollagen (ICTP)]. IGF system components show a trend to increase both in patients progressing on AG and in patients progressing on other NSS-AIs. Such an increase depends on the wash-out length from the previous treatment and is strictly linked to the circulating oestrogen levels. Serum IL-6 and sIL-6-R are mainly related to the patients' clinical outcome. Bone formation (BGP and BAP) and bone resorption (ICTP) markers seem to be at equilibrium with oestrogen levels when starting EXE and do not appear to

be uncoupled over treatment. The observed variations seem to be mainly linked to the circulating oestrogen levels rather than directly to the way of action of the AI employed.

L5 ANSWER 5 OF 14 MEDLINE on STN  
AN 2002492826 MEDLINE  
DN PubMed ID: 12355483  
TI The insulin-like growth factor binding proteins in uncultured human cartilage: increases in insulin-like growth factor binding protein 3 during osteoarthritis.  
AU Morales Teresa I  
CS Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts 02114, USA.. tmorales@partners.org  
NC R03-AG-16390 (NIA)  
SO Arthritis and rheumatism, (2002 Sep) 46 (9) 2358-67.  
Journal code: 0370605. ISSN: 0004-3591.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 200211  
ED Entered STN: 20021001  
Last Updated on STN: 20021213  
Entered Medline: 20021108  
AB OBJECTIVE: To assess changes in the insulin-like growth factor binding proteins (IGFBPs) in uncultured cartilage during stages of osteoarthritis (OA), and to determine if OA cartilage is capable of autocrine secretion of IGFBPs. METHODS: Articular cartilage was dissected from fibrillated and nonfibrillated sites of 11 human femoral heads, and extracted in buffer containing 8M urea. IGFBPs were identified by immunoprecipitation and subsequent analysis by (125)I-IGF-2 Western ligand blotting (WLB), radioimmunoassay, or 2-site immunoradiometric assay (IRMA). IGFBPs were assessed in cartilage extracts by WLB. IGFBP-3 content was determined by IRMA and synthesis by metabolic labeling with (35)S-cysteine in organ cultures. RESULTS: Sample grouping into 3 distinct OA strata was supported by gross pathology of the femoral heads, histologic grading of cartilage slices, and biochemical analysis of the glycosaminoglycan and protein content of the extracts. Group I was normal/mild OA, group II was intermediate OA, and group III was severe OA. IGFBP-2 was present in all samples, IGFBP-4 in sporadic samples, and BP-3 in group II-III samples. By IRMA, group I had a mean +/- SD of 6.26 +/- 2.6 ng IGFBP-3/mg soluble protein (IGFBP-3) (n = 6), group II had a mean +/- SD 14 +/- 7.5 IGFBP-3 (n = 10), and group III had a mean +/- SD 17.03 +/- 8.94 IGFBP-3 (n = 6). Analysis of variance showed group differences (F[3,19] = 3.84, P = 0.04), and post hoc tests revealed that IGFBP-3 levels were higher for group III versus group I (P = 0.04). OA cartilage synthesized IGFBP-3. CONCLUSION: Increases in net cartilage content of IGFBP-3 occurred in intact OA cartilage, reaching statistically significant elevation in severe disease. There was autocrine IGFBP-3 production in OA cartilage.

L5 ANSWER 6 OF 14 MEDLINE on STN  
AN 2001012500 MEDLINE  
DN PubMed ID: 10951195  
TI O-glycosylation of insulin-like growth factor (IGF) binding protein-6 maintains high IGF-II binding affinity by decreasing binding to glycosaminoglycans and susceptibility to proteolysis.  
AU Marinaro J A; Neumann G M; Russo V C; Leeding K S; Bach L A  
CS University of Melbourne, Department of Medicine, Austin & Repatriation Medical Centre, Heidelberg, Victoria, Australia.  
SO European journal of biochemistry / FEBS, (2000 Sep) 267 (17) 5378-86.  
Journal code: 0107600. ISSN: 0014-2956.  
CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200010  
 ED Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20001031

AB Insulin-like growth factor binding protein-6 (IGFBP-6) is an O-linked glycoprotein which specifically inhibits insulin-like growth factor (IGF)-II actions. The effects of O-glycosylation of IGFBP-6 on binding to glycosaminoglycans and proteolysis, both of which reduce the IGF binding affinity of other IGFBPs were studied. Binding of recombinant human nonglycosylated (n-g) IGFBP-6 to a range of glycosaminoglycans in vitro was approximately threefold greater than that of glycosylated (g) IGFBP-6. When bound to glycosaminoglycans, IGFBP-6 had approximately 10-fold reduced binding affinity for IGF-II. Exogenously added n-gIGFBP-6 but not gIGFBP-6 also bound to partially purified rat PC12 phaeochromocytoma membranes. Binding of n-gIGFBP-6 was inhibited by increasing salt concentrations, which is typical of glycosaminoglycan interactions. O-glycosylation also protected human IGFBP-6 from proteolysis by chymotrypsin and trypsin. Proteolysis decreased the binding affinity of IGFBP-6 for IGF-II, even with a relatively small reduction in apparent molecular mass as observed with chymotrypsin. Analysis by ESI-MS of IGFBP-6 following limited chymotryptic digestion showed that a 4.5-kDa C-terminal peptide was removed and peptide bonds involved in the putative high affinity IGF binding site were cleaved. The truncated, multiply cleaved IGFBP-6 remained held together by disulphide bonds. In contrast, trypsin cleaved IGFBP-6 in the mid-region of the molecule, resulting in a 16-kDa C-terminal peptide which did not bind IGF-II. These results indicate that O-glycosylation inhibits binding of IGFBP-6 to glycosaminoglycans and cell membranes and inhibits its proteolysis, thereby maintaining **IGFBP-6** in a high-affinity, **soluble** form and so contributing to its inhibition of IGF-II actions.

L5 ANSWER 7 OF 14 MEDLINE on STN  
 AN 1999046935 MEDLINE  
 DN PubMed ID: 9831072  
 TI Insulin-like growth factor binding proteins localize to discrete cell culture compartments in periosteal and osteoblast cultures from fetal rat bone.

AU Chen Y; Shu H; Ji C; Casinghino S; Kim K; Gundberg C M; Centrella M; McCarthy T L  
 CS Department of Surgery, Yale University School of Medicine, New Haven, Connecticut 06520, USA.  
 NC DK47421 (NIDDK)  
 SO Journal of cellular biochemistry, (1998 Dec 1) 71 (3) 351-62.  
 Journal code: 8205768. ISSN: 0730-2312.  
 CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Space Life Sciences  
 EM 199901  
 ED Entered STN: 19990128  
 Last Updated on STN: 20020124  
 Entered Medline: 19990113

AB Insulin-like growth factor (IGF)-I and IGF-II are expressed at biologically effective levels by bone cells. Their stability and activity are modulated by coexpression of IGF binding proteins (IGFBPs). Secreted IGFBPs may partition to soluble, cell-associated, and matrix-bound compartments. Extracellular localization may sequester, store, or present IGFs to appropriate receptors. Of the six IGFBPs known, rat osteoblasts synthesize all but IGFBP-1. Of these, IGFBP-3, -4, and -5 mRNAs are

induced by an increase in cAMP. Little is known about extracellular IGFBP localization in bone and nothing about IGFBP expression by nonosteoblastic periosteal bone cells. We compared basal IGFBP expression in periosteal and osteoblast bone cell cultures and assessed the effects of changes in cAMP-dependent protein kinase A or protein kinase C. Basal IGFBP gene expression differed principally in that more IGFBP-2 and -5 occurred in osteoblast cultures, and more IGFBP-3 and -6 occurred in periosteal cultures. An increase in cAMP enhanced **IGFBP-3, -4, and -5 mRNA** and accordingly increased **soluble IGFBP-3, -4, and -5** and matrix-bound **IGFBP-3 and -5** in both bone cell populations. In contrast, protein kinase C activators suppressed IGFBP-5 mRNA, and its basal protein levels remained very low. We also detected low Mr bands reactive with antisera to IGFBP-2, -3, and -5, suggesting proteolytic processing or degradation. Our studies reveal that various bone cell populations secrete and bind IGFBPs in selective ways. Importantly, inhibitory IGFBP-4 does not significantly accumulate in cell-associated compartments, even though its secretion is enhanced by cAMP. Because IGFBPs bind IGFs less tightly in cell-bound compartments, they may prolong anabolic effects by agents that increase bone cell cAMP.

L5 ANSWER 8 OF 14 MEDLINE on STN  
 AN 97456288 MEDLINE  
 DN PubMed ID: 9311602  
 TI Surface-bound plasmin induces selective proteolysis of insulin-like-growth-factor (IGF)-binding protein-4 (IGFBP-4) and promotes autocrine IGF-II bio-availability in human colon-carcinoma cells.  
 AU Remacle-Bonnet M M; Garrouste F L; Pommier G J  
 CS Unite Interactions entre Systemes Proteiques et Differentiation dans la Cellule Tumorale, Faculte de Medecine, URA CNRS 1924, Marseille, France.  
 SO International journal of cancer. Journal international du cancer, (1997 Sep 4) 72 (5) 835-43.  
 Journal code: 0042124. ISSN: 0020-7136.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199710  
 ED Entered STN: 19971224  
 Last Updated on STN: 20000303  
 Entered Medline: 19971031  
 AB Limited proteolysis of insulin-like-growth-factor (IGF)-binding proteins (IGFBPs) represents a key process to modulate IGF bio-availability at the cellular level. In human colon carcinomas, urokinase-type plasminogen activator (u-PA) produced by stroma cells can bind to cancer-cell-associated u-PA receptor (u-PAR), and then catalyze the conversion of plasminogen (Pg) into plasmin (Pm). We therefore investigated the interplay between the IGF and Pm systems in the HT29-D4 human colon-carcinoma-cell model. HT29-D4 cells secreted IGF-II totally complexed to IGFBP-2, IGFBP-4 and IGFBP-6. Approximately 15% of IGFBP-4 was associated with the extracellular matrix. HT29-D4 cells produced neither u-PA- nor IGFBP-specific proteases. However, activation of Pm at the HT29-D4 cell surface obtained by the sequential addition of exogenous u-PA and Pg to mimic the stromal complementation induced selective proteolysis targeted to IGFBP-4 only (>95%). **IGFBP-2 and IGFBP-6**, though sensitive to proteolysis by **soluble** Pm, were not altered by cell-bound Pm. IGFBP-4 proteolysis yielded 18- and 14-kDa immunoreactive fragments which were not detectable by Western ligand blotting, indicating that they bound IGF-II with poor affinity. Release of IGF-II from IGF-II-IGFBP complexes after IGFBP-4 proteolysis by cell-bound Pm was indicated by the observation that approximately 20% of the 125I-IGF-II initially associated with endogenous IGFBP in reconstituted complexes was transferred to HT29-D4 cell-surface IGF-I receptors. These results suggest that IGFBP-4 proteolysis by

cell-bound Pm can promote autocrine/paracrine IGF-II bio-availability in colon-cancer cells. This may have important consequences on the behavior of cancer cells at the interface between stroma and malignant cells in carcinomas of the colon in vivo.

L5 ANSWER 9 OF 14 MEDLINE on STN  
AN 97375474 MEDLINE  
DN PubMed ID: 9231791  
TI Interleukin-6 and its soluble receptor regulate the expression of insulin-like growth factor binding protein-5 in osteoblast cultures.  
AU Franchimont N; Durant D; Canalis E  
CS Department of Research, Saint Francis Hospital and Medical Center, Hartford, Connecticut 06105, USA.  
NC DK-42424 (NIDDK)  
SO Endocrinology, (1997 Aug) 138 (8) 3380-6.  
Journal code: 0375040. ISSN: 0013-7227.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 199708  
ED Entered STN: 19970902  
Last Updated on STN: 19980206  
Entered Medline: 19970815  
AB Interleukin-6 (IL-6), a cytokine produced by bone cells, is known to influence bone resorption by stimulating the development of osteoclasts from precursor cells and to have mitogenic actions on osteoblastic cells. Insulin-like growth factors (IGFs) are important local regulators of bone formation, and IGF binding protein (IGFBP)-5 stimulates bone cell growth and enhances the effects of IGF-I. We tested the effects of IL-6 in the presence and absence of its **soluble** receptor (sIL-6R) on **IGFBP-5** expression in cultures of osteoblast-enriched cells from 22-day-old fetal rat calvariae (Ob cells). When tested individually, IL-6 and sIL-6R had a modest stimulatory effect on IGFBP-5 messenger RNA (mRNA) levels. In contrast, when IL-6 and sIL-6R were tested in combination, they caused a considerable increase in IGFBP-5 mRNA levels, and IL-6 at 100 ng/ml and sIL-6R at 125 ng/ml increased IGFBP-5 transcripts by 5- to 7-fold after 24 h. The effect of IL-6 and sIL-6R on IGFBP-5 transcripts was not blocked by indomethacin, but cycloheximide markedly inhibited IGFBP-5 mRNA levels in control and treated cultures. IL-6 and sIL-6R did not modify the decay of IGFBP-5 mRNA in transcriptionally arrested Ob cells, and stimulated the rate of IGFBP-5 transcription as demonstrated by a nuclear run-on assay. IL-6 and sIL-6R did not increase intact IGFBP-5 levels in the extracellular matrix and increased IGFBP-5 fragments in the culture medium. Conditioned medium from Ob cells induced the proteolytic fragmentation of an IGFBP-5 standard, an effect that was accelerated and enhanced by conditioned medium from IL-6/sIL-6R-treated cultures and prevented by metalloprotease inhibitors. In conclusion, IL-6, in the presence of sIL-6R, stimulates IGFBP-5 mRNA expression in Ob cells by transcriptional mechanisms, and accelerates the fragmentation of the protein.

L5 ANSWER 10 OF 14 MEDLINE on STN  
AN 96159065 MEDLINE  
DN PubMed ID: 8591997  
TI Intact insulin-like growth factor binding protein-5 (IGFBP-5) associates with bone matrix and the **soluble** fragments of **IGFBP-5** accumulated in culture medium of neonatal mouse calvariae by parathyroid hormone and prostaglandin E2-treatment.  
AU Hakeda Y; Kawaguchi H; Hurley M; Pilbeam C C; Abreu C; Linkhart T A; Mohan S; Kumegawa M; Raisz L G  
CS Division of Endocrinology and Metabolism, University of Connecticut Health Center, Farmington 06030, USA.

SO Journal of cellular physiology, (1996 Feb) 166 (2) 370-9.  
Journal code: 0050222. ISSN: 0021-9541.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Space Life Sciences

EM 199604

ED Entered STN: 19960418

Last Updated on STN: 20000303

Entered Medline: 19960401

AB We examined the distribution of insulin-like growth factor binding proteins (IGFBPs) in cultured neonatal mouse calvariae. IGFBP-3 and -4 were predominantly found in the conditioned medium. IGFBP-2 was partitioned between conditioned medium and bone and extracellular matrix (BECM), while intact (31-kDa) IGFBP-5 was most abundant in BECM extracts. After treatment with parathyroid hormone (PTH,  $10^{-8}$  M) or prostaglandin E2 (PGE2,  $10^{-6}$  M), immunoreactive IGFBP-5 accumulated in the conditioned medium in a 21-kDa form which did not bind IGF-I on Western ligand blots. PTH and PGE2 did not alter the level of steady-state IGFBP-5 mRNA, nor markedly stimulate IGFBP-5 synthesis in the calvariae, and thus accumulation of 21-kDa IGFBP-5 was largely due to release from BECM. This accumulation of truncated IGFBP-5 in the conditioned medium was not dependent on osteoclastic bone resorption, since it was not blocked by calcitonin or a bisphosphonate which inhibited PTH- and PGE2-stimulated  $^{45}\text{Ca}$ -release. The conditioned medium from PTH- or PGE2-treated cultures degraded recombinant human IGFBP-5 into lower molecular weight fragments. Addition of IGF-1 at  $10^{-8}$  M into the culture resulted in accumulation of native 31-kDa IGFBP-5. However, even in the presence of IGF-1, the native IGFBP-5 was degraded and the 21-kDa product accumulated in the culture medium. These results suggested a possible proteolytic mechanism for 21-kDa IGFBP-5 accumulation, responsive to PTH and PGE2. Aprotinin, leupeptin, cystatin, and bestatin did not inhibit the effects of PTH and PGE2 in the cultures. The localization of IGFBP-5 in BECM and its release and proteolysis induced by PTH and PGE2 could play a role in the local regulation of bone metabolism.

L5 ANSWER 11 OF 14 MEDLINE on STN

AN 95206421 MEDLINE

DN PubMed ID: 7534873

TI Insulin-like growth factor binding protein-1 is pre-synaptic at mouse neuromuscular synapses and is transported in nerve.

AU Ma J; Yang S X; Ho G J; Festoff B W

CS Neurobiology Research Lab (151R), VA Medical Center, Kansas City, MO 64128.

NC P30 AG10182 (NIA)

SO Neurochemical research, (1994 Nov) 19 (11) 1363-8.

Journal code: 7613461. ISSN: 0364-3190.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199504

ED Entered STN: 19950504

Last Updated on STN: 19960129

Entered Medline: 19950426

AB In a previous study, we localized insulin-like growth factor binding protein 1 (IGFBP-1) to mouse neuromuscular junctions, and intramuscular nerves. To determine if pre-synaptic accumulation of IGFBP-1 occurred, we used double ligation of sciatic nerve in adult mice at different time points. IGFBPs were detected by Western ligand blot (WLB) with  $^{125}\text{I}$ -IGF-I. WLB and Western immunoblot (WIB) analysis of extracts from double-ligated nerves showed a delayed (6 days) increase of IGFBP-1 in the **soluble** fraction between the ligatures



and distal to the distal ligature. For comparison we evaluated transport of neurofilament components, using WIB and confirmed the primarily anterograde transport of these intraaxonal proteins. These data suggest that expression of IGFBP-1 is both by activated Schwann cells as well as retrograde axonal transport with likely entry into the axon at the synapse.

L5 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:187505 CAPLUS

DN 140:351095

TI Zinc partitions IGFs from **soluble** IGF binding proteins ( **IGFBP**)-5, but not **soluble IGFBP**-4, to myoblast IGF type 1 receptors

AU McCusker, R. H.; Novakofski, J.

CS The Department of Animal Sciences, Laboratory for Developmental Endocrinology, The University of Illinois, Urbana, IL, 61801, USA

SO Journal of Endocrinology (2004), 180(2), 227-246

CODEN: JOENAK; ISSN: 0022-0795

PB Society for Endocrinology

DT Journal

LA English

AB Zinc (Zn<sup>2+</sup>), a multifunctional micronutrient, was recently shown to lower the affinity of cell-associated insulin-like growth factor (IGF) binding protein (IGFBP)-3 and IGFBP-5 for both IGF-I and IGF-II, but to increase the affinity of the cell surface type 1 IGF receptor (IGF-1R) for the same two ligands. However, there is a need for data concerning the effects of Zn<sup>2+</sup> on soluble IGFBPs and the type 2 IGF receptor (IGF-2R). In the current work, the authors demonstrate that Zn<sup>2+</sup> affects the affinity of IGFBP-5 secreted by myoblasts but not IGFBP-4. Zn<sup>2+</sup>, at physiol. levels, depressed binding of both IGF-I and IGF-II to IGFBP-5, affecting 125I-IGF-I more than 125I-IGF-II. Both 125I-IGF-I and 125I-IGF-II bound to high and low affinity sites on IGFBP-5. Zn<sup>2+</sup> converted the high affinity binding sites of IGFBP-5 into low affinity binding sites. An IGF-I analog, 125I-R3-IGF-I, did not bind to the soluble murine IGFBP-5. Zn<sup>2+</sup> also decreased the affinity of the IGF-2R on L6 myoblasts. In contrast, Zn<sup>2+</sup> increased IGF-I, IGF-II and R3-IGF-I binding to the IGF-1R by increasing ligand binding affinity on both P2A2a-LISN and L6 myoblasts. Soluble IGFBP-5 and IGFBP-4 depressed the binding of 125I-IGF-I and 125I-IGF-II to the IGF-1R, but did not affect binding of 125I-R3-IGF-I. By depressing the association of the IGFs with soluble IGFBP-5, Zn<sup>2+</sup> partitioned

125I-IGF-I and 125I-IGF-II from soluble IGFBP-5 onto cell surface IGF-1Rs. This effect is not seen when soluble L6-derived IGFBP-4 is present in extracellular fluids. The authors introduce a novel mechanism by which the trace micronutrient Zn<sup>2+</sup> may alter IGF distribution, i.e., Zn<sup>2+</sup> acts to increase IGF-1R binding at the expense of IGF binding to soluble IGFBP-5 and the IGF-2R.

RE.CNT 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:873370 CAPLUS

DN 140:123136

TI Zinc partitions insulin-like growth factors (IGFs) from **soluble** IGF binding protein (**IGFBP**)-5 to the cell surface receptors of BC3H-1 muscle cells

AU McCusker, Robert H.; Novakofski, Jan

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SO Journal of Cellular Physiology (2003), 197(3), 388-399

CODEN: JCLLAX; ISSN: 0021-9541

PB Wiley-Liss, Inc.

DT Journal

LA English

AB Zinc ( $Zn^{2+}$ ) is a multifunctional micronutrient. The list of functions for this micronutrient expanded with the recent discovery that  $Zn^{2+}$  retains insulin-like growth factors binding proteins (IGFBPs) on the surface of cultured cells, lowers the affinity of cell-associated IGFBPs, and increases the affinity of the cell surface insulin-like growth factor (IGF)-type 1 receptor (IGF-1R). However, currently there is no information concerning the effect of  $Zn^{2+}$  on soluble IGFBPs. In the current study, the soluble

IGFBP-5

secreted by BC3H-1 cells is shown to bind approx. 50% more [ $^{125}I$ ]-IGF-II than [ $^{125}I$ ]-IGF-I at pH 7.4.  $Zn^{2+}$  is shown to depress the binding of both IGF-I and IGF-II to soluble secreted IGFBP-5; [ $^{125}I$ ]-IGF-I binding is affected more so than [ $^{125}I$ ]-IGF-II binding.  $Zn^{2+}$  acts by lowering the affinity ( $K_a$ ) of IGFBP-5 for the IGFs. Scatchard plots are non-linear indicating the presence of high and low affinity binding sites;  $Zn^{2+}$  affects only binding to the high affinity site. In contrast,  $Zn^{2+}$  increases the affinity by which either [ $^{125}I$ ]-IGF-I or [ $^{125}I$ ]-R3-IGF-I binds to the IGF-1R, but depresses [ $^{125}I$ ]-IGF-II binding to the IGF-type 2 receptor (IGF-2R) on BC3H-1 cells. By depressing the association of the IGFs with soluble IGFBPs,  $Zn^{2+}$  is shown to repartition either [ $^{125}I$ ]-IGF-I or [ $^{125}I$ ]-IGF-II from soluble IGFBP-5 onto cell surface IGF receptors.  $Zn^{2+}$  was active at physiol. doses depressing IGF binding to IGFBP-5 and the IGF-2R at 15-20  $\mu M$ . Hence, a novel mechanism is further characterized by which the trace micronutrient  $Zn^{2+}$  could regulate IGF activity.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1996:81367 CAPLUS

DN 124:107668

TI Intact insulin-like growth factor binding protein-5 (IGFBP-5) associates with bone matrix and the **soluble** fragments of **IGFBP-5** accumulated in culture medium of neonatal mouse calvariae by parathyroid hormone and prostaglandin E2-treatment

AU Hadedá, Yoshiyuki; Kawaguchi, Hiroshi; Hurley, Marja; Pilbeam, Carol C.; Abreu, Christine; Linkhart, Thomas A.; Mohan, Subburaman; Kumegawa, Masayoshi; Raisz, Lawrence G.

CS Div. Endocrinol. Metabolism, Univ. Connecticut Health Cent., Farmington, CT, 06030, USA

SO Journal of Cellular Physiology (1996), 166(2), 370-9  
CODEN: JCLLAX; ISSN: 0021-9541

PB Wiley-Liss

DT Journal

LA English

AB The authors examined the distribution of insulin-like growth factor binding proteins (IGFBPs) in cultured neonatal mouse calvariae. IGFBP-3 and -4 were predominantly found in the conditioned medium. IGFBP-2 was partitioned between conditioned medium and bone and extracellular matrix (BECM), while intact (31-kDa) IGFBP-5 was most abundant in BECM exts. After treatment with parathyroid hormone (PTH,  $10^{-8}$  M) or prostaglandin E2 (PGE2,  $10^{-6}$  M), immunoreactive IGFBP-5 accumulated in the conditioned medium in a 21-kDa form which did not bind IGF-I on Western ligand blots. PTH and PGE2 did not alter the level of steady-state IGFBP-5 mRNA, nor markedly stimulate IGFBP-5 synthesis in the calvariae, and thus accumulation of 21-kDa IGFBP-5 was largely due to release from BECM. This accumulation of truncated IGFBP-5 in the conditioned medium was not dependent on osteoclastic bone resorption, since it was not blocked by calcitonin or a bisphosphonate which inhibited PTH- and PGE2-stimulated  $^{45}Ca$ -release. The conditioned medium from PTH- or PGE2-treated cultures degraded recombinant human IGFBP-5 into lower mol. weight fragments. Addition of IGF-I at  $10^{-8}$  M into the culture resulted in accumulation of native 31-kDa IGFBP-5. However, even in the presence of IGF-I, the native IGFBP-5 was degraded and the 21-kDa product accumulated in the culture

medium. These results suggested a possible proteolytic mechanism for 21-kDa IGFBP-5 accumulation, responsive to PTH and PGE2. Aprotinin, leupeptin, cystatin, and bestatin did not inhibit the effects of PTH and PGE2 in the cultures. The localization of IGFBP-5 in BECM and its release and proteolysis induced by PTH and PGE2 could play a role in the local regulation of bone metabolism

=> d his

(FILE 'HOME' ENTERED AT 12:48:24 ON 12 APR 2005)

FILE 'MEDLINE, USPATFULL, CAPLUS' ENTERED AT 12:48:45 ON 12 APR 2005

L1	11124 S IGFBP OR INSULIN GROWTH FACTOR BINDING PROTEIN
L2	0 S L1 (5A) SHEDDING
L3	0 S L1 (5A) SHED
L4	2879 S L1 (5A) (5 OR 6)
L5	14 S L4 (5A) (SOLUBLE)